Treatment outcomes in patients with multidrug-resistant tuberculosis in north-west Ethiopia

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Abstract

OBJECTIVE Multidrug-resistant tuberculosis (MDR-TB) is an emerging public health problem in Ethiopia. The aim of this study was to assess MDR-TB treatment outcomes and determine predictors of poor treatment outcomes in north-west Ethiopia.

METHODS A retrospective cohort study was conducted using all MDR-TB patients who were enrolled at Gondar University Hospital since the establishment of the MDR-TB programme in 2010. A Cox proportional hazard model was used to identify the predictors of time to poor treatment outcomes, which were defined as death or treatment failure.

RESULTS Of the 242 patients who had complete records, 131 (54%) were cured, 23 (9%) completed treatment, 31 (13%) died, four (2%) experienced treatment failure, 27 (11%) were lost to follow-up, six (2%) transferred out, and 20 (8%) were still on treatment at the time of analysis. The overall cumulative probability survival of the patients at the end of treatment (which was 24 months in duration) was 80% (95% CI: 70%, 87%). The proportion of patients with poor treatment outcomes increased over time from 6% per person-year (PY) during 2010–2012, to 12% per PY during 2013–2015. The independent predictors of time to poor treatment outcome were being anaemic [AHR = 4.2; 95% CI: 1.1, 15.9] and being a farmer [AHR = 2.2; 95% CI: 1.0, 4.9].

CONCLUSIONS Overall, in north-west Ethiopia, the MDR-TB treatment success rate was high. However, poor treatment outcomes have gradually increased since 2012. Being a farmer and being anaemic were associated with poor treatment outcomes. It would be beneficial to assess other risk factors that might affect treatment outcomes such as co-infection with malaria, poverty and other socio-economic and biological risk factors.

keywords multidrug-resistant tuberculosis, tuberculosis, outcomes, Ethiopia

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a major public health problem globally and is an obstacle for national TB control programmes [1]. MDR-TB is defined as TB that is resistant to at least the two most effective first-line anti-TB drugs, isoniazid (INH) and rifampicin (RIF) [1]. According to the WHO 2015 Global Tuberculosis Report, 480 000 MDR-TB cases were estimated to be diagnosed globally, and of these, 190 000 (39.5%) died as a result of it in 2014 [2]. Furthermore, WHO estimated that only 25.6% of MDR-TB cases were diagnosed and only 23.1% of cases received access to MDR-TB treatment globally, and of those who had received MDR-TB treatment, only 50% were successfully treated [3, 4].

Ethiopia is a high TB-burden country and reports approximately 140 000 cases of TB each year [5]. The MDR-TB burden in Ethiopia is not well known, except for estimates based on the first-round drug resistance survey (DRS) conducted in 2003–2005 which showed that 1.6% and 11.8% of new and previously treated TB cases had MDR-TB, respectively [6, 7]. MDR-TB was reported in Ethiopia 30 years ago in a hospital-based study [8], and since this time, the estimated number of patients with MDR-TB has increased exponentially. Whereas 145 MDR-TB cases were reported in 2007, this number had risen to 558 in 2013 [2]. Ethiopia ranks

17th in the list of the world's 27 high-burden countries for multidrug-resistant and extensive drug-resistant tuberculosis (M(X) DR-TB), with more than 2200 estimated MDR-TB patients every year [2].

As a result, the Ethiopian government has identified MDR-TB as one of the country's priority public health problems. In 2009, the government initiated a national MDR-TB treatment programme, with two designated MDR-TB treatment centres: one in Gondar University Hospital, Gondar, and the other at St. Peter's Tuberculosis Specialized Hospital, Addis Ababa. Since this time, 10 additional MDR-TB treatment centres have opened in the country [5]. Acid-fast bacillus (AFB) microscopy is widely used across the country for TB diagnostic and treatment follow-up services. However, culture and drug susceptibility testing (DST) is only available in national and regional laboratory centres and requires referral of either samples or patients. Phenotypic DST and line-probe assay (i.e. Geno Type MTBDRplus V.2.0, HAIN Life, Science, Nehren, Germany) are used at national and regional reference laboratories to identify MDR-TB cases. Patients diagnosed with MDR-TB are eligible to get treatment service free of charge [5, 9].

Improving MDR-TB treatment outcomes is one of the five priority actions recommended by WHO to address the global MDR-TB crisis [3], with a target of 75% treatment success by the end of 2015 [10]. Many countries currently fall short of this ambitious target. The predictors of favourable treatment outcomes for people with MDR-TB vary according to the context [11–13]. There are few studies on MDR-TB treatment outcomes in resource-constrained settings and in high MDR-TB-burden countries [14, 15]. The purpose of this study was to assess MDR-TB treatment outcomes, predictors of time to poor MDR-TB treatment outcome and temporal trends in MDR-TB treatment outcomes among patients who were enrolled in Gondar University Hospital MDR-TB Treatment Centre since its establishment in September 2010.

Methods

Study setting and participants

A retrospective cohort study was conducted at Gondar University Hospital among MDR-TB patients who registered at the MDR-TB treatment centre, between September 2010 and August 2015. Gondar University Hospital is the oldest hospital in the country and is located in north-west Ethiopia. It provides healthcare services for a catchment population of approximately 5 million people in North Gondar and the neighbouring region. Patients are enrolled in the MDR-TB treatment centre if they have [1] bacteriological evidence of rifampicin resistance (RR), determined by culture; [2] bacteriological evidence of MDR-TB, determined by a line-probe assay (i.e. Geno Type MTBDRplus V.2.0, HAIN Life, Science), Gene Xpert or conventional drug susceptibility testing (DST); or [3] clinical evidence of MDR-TB based on multiple treatment failures, or a history of contact with someone with MDR-TB. All patients enrolled at the MDR-TB treatment centre are eligible for treatment [9].

Treatment regimen

At the hospital, MDR-TB treatment is prescribed based on the recommendations of the Ethiopian Federal Ministry of Health National MDR-TB Guideline, which is based on recommendations from WHO guidelines [16]. All newly diagnosed MDR-TB patients receive a standardised regimen of first- and second-line TB drugs that consists of an 8-month intensive phase with a combination of pyrazinamide (Z), capreomycin (CM), levofloxacin (Lfx) and prothionamide (Pto) or ethionamide (Eto) and cycloserine (Cs), a 12-month continuation phase with a combination of pyrazinamide (Z), levofloxacin (Lfx), prothionamide (Pto) or ethionamide (Eto), and cycloserine (Cs) [9]. However, certain groups of MDR-TB patients cannot receive the standardised regimen, requiring either a modification of the regimen or dose adjustment [9]. These groups include pregnant women, children, patients with comorbidities such as chronic renal dysfunction, HIV or liver disease, patients who report household contact with other rifampicin-resistant (RR)/MDR or XDR-TB patients, and patients who have a history of prior exposure to second-line TB drugs [9].

Data collection

Data were extracted from patients' MDR-TB registration books and medical records. The registration book contained a number of variables including socio-demographic characteristics (age, sex, residence, marital status, educational status, occupation, religion, treatment supporter), clinical variables (HIV status and other comorbidities, site of TB disease, number of previous TB treatments, initial MDR-TB regimen, initial regimen change, vitamin B6 supplementation, initial sputum and culture result, adverse drug effects, height and weight) and laboratory profile (haemoglobin (Hgb), alanine transaminase (ALT), aspartate transaminase (AST), creatinine, serum potassium (K) level and white blood cell (WBC) count). Data were collected by four healthcare officers who were working in the MDR-TB treatment centre, and who were

trained in study procedures. The collected data from the registration books were cross-checked with the medical records of the patients by the investigators.

Treatment outcomes

MDR-TB treatment outcomes were assigned as per the definitions in the Ethiopian national TB guidelines, which have been adopted wholly from the WHO definitions and reporting framework for TB guidelines as cured, treatment completed, treatment failed, died, lost to follow-up and not evaluated [9, 17]. A patient was classified as cured if the patient completed treatment without evidence of treatment failure and if they had three or more consecutive negative cultures taken at least 30 days apart, after the intensive phase. Treatment completion was defined as completed treatment, without evidence of failure but with no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase. Treatment failure was defined as treatment terminated or a need for permanent regimen change of at least two anti-TB drugs because of a lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative after intensive phase, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions. Lost to follow-up referred to interruption of a patient's treatment for 2 consecutive months or more. Death referred to death for any reason during the course of treatment. A patient for whom no treatment outcome was assigned either due to being transferred out to other facility or still on treatment was classified as not evaluated.

In this study, treatment success was defined as the proportion of all patients who were taking their MDR-TB treatment for the recommended duration and who were declared as either cured or completed (excluding non-evaluated patients). A poor treatment outcome was defined as the proportion of all patients who died or failed treatment excluding those who were not evaluated.

The outcome of interest (events) for the survival analysis was 'death' or 'treatment failure', whichever came first. Combined, these two events represented poor treatment outcomes. Patients were considered as censored if they had the TB treatment outcome of cured, completed, transferred out or lost to follow-up or were still on treatment at the end of the study. To include the censored observations in the analysis, we calculated a censored survival time from the start date of treatment (T0) to [1] the date of data collection for patients still on treatment, [2] the last known date of observation for the patients lost to follow-up or transferred out and [3] the date declaration of cure or treatment completion. The follow-up time (FT) was the time from T0 to the date of event or censoring. The time to event survival time (ST) was the time from T0 to the date when the patient experienced an event (T1), in this case death or treatment failure. The treatment outcome was coded as 1 if the event occurred at time Ti and 0 if the event had not occurred (i.e. if it was censored) at time (Ti). The overall survival of the patients was analysed and measured from T0 to the date of failure or death, whichever came first (Figure 1). Based on the WHO definition, patients were considered as anaemic if their haemoglobin concentration was <120 g/l [18].

Data analysis

Data were checked for completeness and entered into a form designed in EPI Info version 3.5.3. Data were then exported to STATA version 14.1 [19] for analysis. Categorical variables were summarised by counts and percentages, and the differences between groups were compared using Pearson's chi-square (χ^2) or Fisher's exact test, where appropriate. Normally distributed continuous variables were summarised by their mean and standard deviation (SD), and we used a two-sample independent t-test to compare the mean values. Non-normally distributed continuous variables were summarised by their median and interquartile range (IQR), and we used a Wilcoxon rank-sum test to compare the median values. A Kaplan–Meier (KM) curve was used to estimate the cumulative survival probability and the median 'survival' time of the patients. The log-rank test was used to compare the survival experience of two or more groups of the study subjects. A bivariate Cox proportional hazard model was first fitted, and the variables significant at P-value <0.1 in the bivariate analysis were used in the final multivariable Cox proportional hazard model. Crude and adjusted hazard ratios were calculated to measure time to poor treatment outcomes. The overall adequacy of the general predictive power of the model was measured using Harrell's c index (note: we observed that the c index was 0.7612, which did achieve the 0.70 mark for acceptable discrimination for prognostic model). The Cox proportional hazard assumption was also examined for each covariate and globally using a formal significance test based on the unscaled and scaled Schoenfeld residuals. It was observed that the proportional hazard assumption was justified, because the test was not significant (P = 0.46). In addition, a graphical assessment of proportional hazards was made using log–log survival curves. Data were missing for some patients for height, weight, ALT and AST and;

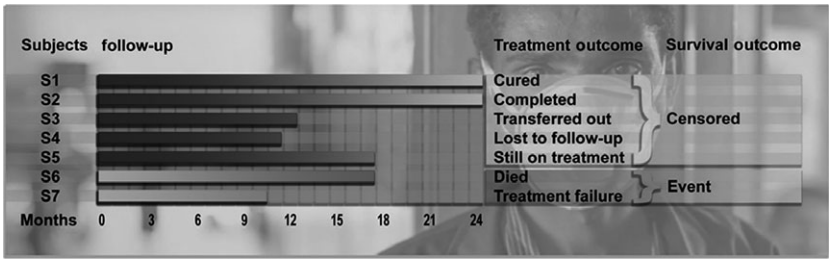


Figure 1 Schematic of survival and treatment outcomes of the follow-up patients included in the study

missing values were imputed as the sex-specific median for these variables.

Ethics approval

Ethical clearance was obtained from the Institutional Review Board of the University of Gondar and from the Australian National University Human Research Ethics Committee. The University of Gondar Hospital provided permission to access the data. As this study used secondary data, informed consent was not obtained from each patient.

Results

Socio-demographic factors

A total of 282 patients were registered and commenced on MDR-TB treatment between 2010 and 2015. Of these, 242 (86%) MDR-TB patients had complete records and were included in the analysis. Half of the patients (123, 50%) were from North Gondar zone, and two-thirds (61%) of the patients were male. The median age of patients was 30 years (range 3–73 years), and patients had low average monthly income (median income 997 Ethiopian Birr, IQR 600–997) (Table 1).

Clinical characteristics

Almost all patients had pulmonary TB 227 (94%) with positive sputum smear results for 194 (80%) and a positive culture result for 131 (54%). There were 13 cases of rifampicin mono-resistance (4.6%), and there were two cases of XDR-TB (0.7%), who both died. The majority of patients (225, 93%) had a history of TB treatment, and the median number of previous TB treatment was 2 (IQR: 2–3). The initial regimens were modified for 15 (6%) of the patients. The reasons for these modifications are not well documented. Psychosis and treatment failure were reported as the most common side effects and reasons for regimen change. At the commencement of treatment, the majority of patients (174, 72%) were underweight (BMI < 18.5 kg/m^2); the mean baseline BMI of the event category was 16.2 km/m^2 ± 2.7 and of the censored category was 17.3 km/m^2 ± 2.6, (*P*-value = 0.02). Similarly, the mean haemoglobin level at baseline for the event category was 12.7 ± 6.4 and for the censored category was 10.6 ± 2.73) (*P*-value = 0.07) (Table 2).

Treatment outcomes

Of the 242 MDR-TB patients, 131 (54%) were cured, 23 (10%) completed treatment, 31 (13%) died, and four (2%) had treatment failure (Table 3). Treatment outcome was assessed for 189 (78%) patients, and the proportion of MDR-TB patients who successfully completed treatment among these patients was 154 (81%). The treatment outcome was not evaluated for 53 (22%) patients because 20 (8%) were still on treatment, six (2%) transferred out to another MDR-TB treatment centre and 27 (11%) were lost to follow-up (Table 3). Poor treatment outcomes were more common among anaemic patients than non-anaemic patients (22% *vs.* 10%, $P = 0.03$) (Table 3). HIV infection was not associated with poorer TB treatment outcomes (20% *vs.* 13% for those with HIV infection and no HIV infection, respectively, $P = 0.57$).

All 242 patients were followed for a median of 20 months (IQR: 14 to 23 months) with a total of 4279 person-months. During this period, 35 poor treatment outcomes occurred: 31 deaths and four treatment failures, resulting in eight poor outcomes per 1000 person-months. The median time to a poor outcome was 5 months (IQR = 2–15 months), indicating poor outcomes occurred during the intensive phase (i.e. the first eight months of MDR-TB treatment).

Patients were lost to follow-up during the intensive phase, after a median time of 7 months (IQR 4–13 months), 14 (52%) within 8 months and seven (26%) between 8–12 months. The reason loss to follow-up was not recorded, but four (15%) developed side effects, with one each developing nausea, vomiting, hypokalaemia and psychosis. All of the lost-to-follow-up patients were

Table 1 Baseline socio-demographic of MDR-TB patients stratified by treatment outcome in north-west Ethiopia from 2010 to 2015

Variables	No. of patients (n = 242)	Treatment outcome		P-value
		Event* (n = 35)	Censored** (n = 207)	
Age at diagnosis (years)				0.1
<18	25 (10.3)	1 (2.9)	24 (11.6)	
19–24	54 (22.3)	6 (17.1)	48 (23.2)	
25–30	59 (24.4)	6 (17.1)	53 (25.6)	
31–40	52 (21.5)	10 (28.6)	42 (20.3)	
≥41	52 (21.5)	12 (34.3)	40 (19.3)	
Sex				0.6
Male	147 (60.8)	20 (57.1)	127 (61.1)	
Female	95 (39.3)	15 (42.9)	80 (38.6)	
Zone of residence				0.9
North Gondar	123 (50.7)	21 (60.0)	102 (49.2)	
South Gondar	48 (19.8)	6 (17.1)	42 (20.2)	
Bahir Dar City	23 (9.5)	2 (5.7)	21 (10.1)	
West Gojjam	14 (5.8)	2 (5.7)	12 (5.8)	
East Gojjam	19 (8.0)	2 (5.7)	17 (8.2)	
North Tigray	15 (6.2)	2 (5.7)	13 (6.2)	
Marital status				0.6
Single	94 (38.8)	11 (31.4)	83 (40.1)	
Married	105 (43.3)	19 (54.3)	86 (41.5)	
Divorced	28 (11.5)	3 (8.6)	25 (12.0)	
Widowed	5 (2.0)	1 (2.9)	4 (1.9)	
Separated	10 (4.1)	1 (2.9)	9 (4.3)	
Level of education				
Unable to read and write	111 (45.8)	21 (60.0)	90 (43.5)	0.4
Primary	77 (31.9)	9 (25.7)	68 (32.8)	
Secondary	32 (13.2)	3 (8.6)	29 (14.0)	
Tertiary	22 (9.1)	2 (5.7)	20 (9.7)	
Occupation				0.04
Government employee	22 (9.1)	1 (2.8)	21 (10.1)	
Self-employed	33 (13.6)	2 (5.7)	31 (14.9)	
Farmer	66 (27.3)	15 (42.8)	51 (24.6)	
Housewife	27 (11.2)	6 (17.1)	21 (10.1)	
Student	39 (16.1)	3 (8.6)	36 (17.4)	
Daily labourer	41 (16.9)	8 (22.9)	33 (15.9)	
Not recorded	14 (5.7)	0	14 (6.8)	
Average monthly income (ETB), Median (IQR)	997 (600–997)	997 (500–997)	997 (600–997)	0.6
Religion				0.3
Orthodox Christian	228 (94.2)	33 (94.3)	195 (94.2)	
Muslim	12 (4.9)	1 (2.8)	11 (5.3)	
Others	2 (0.8)	1 (2.8)	1 (0.5)	
Treatment supporter				0.3
Parents	34 (14.0)	2 (5.7)	32 (15.5)	
Children	22 (9.1)	4 (11.4)	18 (8.7)	
Siblings	42 (17.4)	6 (17.1)	36 (17.4)	
Other relative	42 (17.4)	9 (25.7)	33 (15.9)	
Spouse	26 (10.7)	6 (17.1)	20 (9.7)	
No supporter	58 (23.9)	6 (17.1)	52 (25.1)	
Not recorded	18 (7.4)	2 (5.7)	16 (7.7)	

The P-value was taken from the Pearson's chi-square (χ^2) test or Fisher's exact test, independent t test or Wilcoxon rank-sum (Mann–Whitney) test. ETB, Ethiopian Birr; SD, standard deviation; IQR, interquartile range.
*Event in this study was either death or treatment failure; censored** was either cured, completed, transferred out, default, still on treatment.

Table 2 Baseline clinical characteristics of MDR-TB patients stratified by treatment outcome in north-west Ethiopia from 2010 to 2015

Variables	No. of patients (n = 242)	Treatment outcome		P-value
		Event* (n = 35)	Censored** (n = 207)	
Site of the disease				0.8
Pulmonary	227 (93.8)	33 (94.3)	194 (93.7)	
Extra pulmonary	15 (6.2)	2 (5.7)	13 (6.2)	
BMI, mean (SD)	17.18 ± 2.71	16.23 ± 2.77	17.34 ± 2.68	0.02
Previously treated for TB				0.4
Not treated (new)	17 (7.1)	5 (14.3)	12 (5.8)	
Once	42 (17.5)	7 (20.0)	35 (17.1)	
Twice	109 (45.4)	13 (37.1)	96 (46.8)	
Three times	46 (19.1)	7 (20.0)	39 (19.0)	
Four times and above	26 (10.9)	3 (8.6)	23 (11.2)	
HIV status				0.2
Positive	51 (21.1)	10 (28.6)	41 (19.8)	
Negative	191 (78.9)	25 (71.4)	166 (80.2)	
Any comorbidity				0.2
None recorded	183 (75.6)	22 (62.9)	161 (77.1)	
HIV	51 (21.1)	10 (28.7)	41 (19.8)	
Diabetes mellitus	5 (2.0)	2 (5.7)	3 (1.4)	
Congestive heart failure	1 (0.4)	0	1 (0.9)	
Hypertension	1 (0.4)	0	1 (0.9)	
Hepatitis	1 (0.4)	1 (2.9)	0	
Initial regimen				0.5
Z, E, Cm, Lfx, Eto, Cs	121 (50.2)	15 (42.9)	106 (51.5)	
Z, Cm, Lfx, Eto, Cs	120 (49.8)	20 (57.1)	100 (48.6)	
Was the regimen modified				0.2
Yes	15 (6.2)	4 (11.4)	11 (5.3)	
No	213 (88.0)	28 (80.0)	185 (89.4)	
Not recorded	14 (5.8)	3 (8.6)	11 (5.31)	
Taking vitamin B_6				0.2
Yes	142 (58.92)	24 (68.57)	118 (57.28)	
No	99 (41.08)	11 (31.43)	88 (42.72)	
Initial sputum smear result				0.9
Positive	194 (80.2)	28 (80.0)	166 (80.2)	
Negative	27 (11.2)	4 (11.4)	23 (11.1)	
Not recorded	21 (8.7)	3 (8.6)	18 (8.7)	
Initial culture result				0.1
Positive	131 (54.1)	16 (47.7)	115 (55.6)	
Negative	23 (9.5)	1 (2.9)	22 (10.6)	
Not recorded	88 (36.4)	18 (51.4)	70 (33.8)	
Adverse effects				0.3
Yes	67 (27.7)	12 (34.3)	55 (26.6)	
No	175 (72.3)	23 (65.7)	152 (73.4)	
Haemoglobin (Hgb), mean (SD)	12.42 ± 6.1	10.7 ± 2.73	12.7 ± 6.5	0.07
Alanine transaminase (ALT), median (IQR)	15.7 (11.2–22.2)	15.7 (11–34.3)	15.7 (11.8–22.2)	0.4
Aspartate transaminase (AST), median (IQR)	23.0 (17.4–32.8)	23 (17–33)	23 (20–32)	0.4
Creatinine, mean (SD)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.9
Potassium (K), mean ± SD	3.9 ± 0.7	4.1 ± 1.0	3.9 ± 0.6	0.2
White blood cell count (WBC), mean ± SD	6700 (5300–8200)	6700 (5300–7200)	6700 (5300–8400)	0.6

The P-value was taken from the Pearson's chi-square (χ^2) test or Fisher's exact test, independent t-test or Wilcoxon rank-sum (Mann–Whitney) test. BMI, body mass index; ETB, Ethiopian Birr; SD, standard deviation; IQR, interquartile range; Cm, capreomycin; Lfx, levofloxacin; Pto, prothionamide; Eto, ethionamide; Z, pyrazinamide; (Eto); Cs, cycloserine.
*Event in this study was either death or treatment failure; censored** was either cured, completed, transferred out, default, still on treatment.

taking a regimen containing cycloserine; more than one-third (10, 37%) were from North Gondar Zone, and 21 (78%) were sputum smear positive.

The overall cumulative probability of survival at the end of 6 months was 86% (95% CI: 85.9%, 92.9%) and at the end of 24 months was 80% (95% CI: 70.1%,

Table 3 Treatment outcomes of patients with multidrug-resistant tuberculosis among HIV-infected and HIV-uninfected patients, and anaemic and non-anaemic patients, north-west Ethiopia

Treatment outcome	Total patients $N = 242$ (%)	Patients' HIV status		Anaemia**	
		Infected = 51 (%)	Uninfected = 191 (%)	Anaemia = 90 (%)	No anaemia = 152 (%)
Successful treatment					
Cured	131 (54.1)	29 (56.9)	102 (53.4)	44 (48.9)	87 (57.2)
Completed	23 (9.5)	3 (5.9)	20 (10.5)	6 (6.7)	17 (11.2)
Not evaluated					
Alive*	20 (8.2)	3 (5.9)	17 (8.9)	8 (8.9)	12 (7.9)
Transferred out	6 (2.5)	1 (2.0)	5 (2.6)	1 (1.1)	5 (3.3)
Lost to follow-up	27 (11.1)	5 (8.8)	22 (11.5)	11 (12.2)	16 (10.5)
Poor outcome					
Died	31 (12.8)	9 (17.6)	22 (11.5)	17 (18.9)	14 (9.2)
Treatment failure	4 (1.6)	1 (2.0)	3 (1.6)	3 (3.3)	1 (0.6)

*Those who were on treatment and alive during the study period; **Anaemia is defined as having a haemoglobin concentration less than 120 g/l.

87.0%). The median survival time or the survival time at which the cumulative survival function is equal to 0.5 could not be determined because the largest number of observations was censored (Figure 2). Anaemic patients had a shorter survival time than non-anaemic patients ($P = 0.004$). The cumulative probability survival of anaemic patients at the end of 24 months was 76% (95% CI: 64%, 84%), and the cumulative probability survival of non-anaemic patients at the end of 24 months was 85% (95% CI: 73%, 92%) (Figure 3).

Trends of MDR-TB treatment outcomes

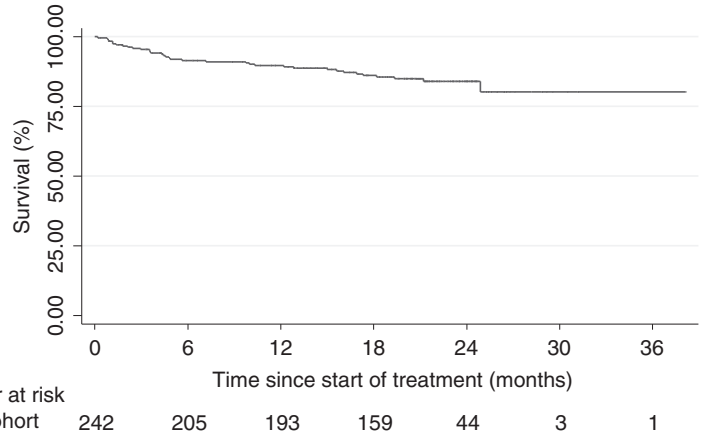
The number of patients who started MDR-TB treatment at Gondar University Hospital increased each year between 2010 and 2013. However, after 2013, the number of MDR-TB patients enrolled at Gondar University Hospital decreased. Proportionally, the poor treatment outcome rate decreased as the number of MDR-TB cases enrolled to the treatment centre increased and increased as the number of MDR-TB cases decreased (correlation coefficient: $r = -0.59$). Generally, the poor treatment outcome rate increased over time since 2012 (Figure 4). Patients who started treatment between 2010 and 2012 showed better treatment outcomes (6%/PY) than patients who started treatment between 2013 and 2015 (12%/PY). Between 2010 and 2012, there were nine deaths but no treatment failures, with a total observation time of 1713 person-months, whereas between 2013 and 2015, there were 21 deaths and four treatment failures, with a total observation time of 2566 person-months. Thus, the incidence rate for the period 2010–2012 was 6%/PY; for the period 2013–2015, it was 12%/PY, giving an incidence rate ratio (IRR) of 2 for 2013–2015 relative to 2010–2012. The proportion of patients who had previously been treated with first-line antituberculosis drugs more than four times increased from 3% in 2010 to 34% in 2013.

Predictors of poor MDR-TB treatment outcomes

In bivariate analysis, low haemoglobin levels (i.e. anaemia), taking vitamin B6, being prescribed an initial regimen with Z+E+Cm+Lfx+Eto+Cs (compared with Z+Cm+Lfx+Eto+Cs) and being a farmer or a daily labourer were significantly associated with time to poor treatment outcome (Table 4). However, in multivariate analyses, being a farmer and being anaemic were the only independent predictors of time to poor treatment outcome (Table 5). Those who had low haemoglobin levels (i.e. patients with anaemia) were more than two times at risk to have a poor treatment outcome at any time than those who had normal haemoglobin levels [AHR = 2.2; 95% CI: 1.0, 4.9]. Similarly, farmers were more than four times at risk to have a poor treatment outcome at any time than employees [AHR = 4.2; 95% CI: 1.1, 15.9].

Discussion

This study was designed to assess treatment outcomes and determine predictors of time to poor treatment outcomes in the first cohort of MDR-TB patients in north-west Ethiopia. We found that the overall cumulative probability of treatment success (i.e. having an outcome of cured or treatment completed) at the end of the treatment (24 months) was 80% (95% CI: 70%, 87%),



Event	*20*	*4*	*7*	*3*	*1*	*0*	*0*
censored	*17*	*8*	*27*	*112*	*40*	*2*	*1*
Survival (%)	*91.4*	*90*	*86*	*84*	*80*	*80*	*80*
95% CI (%)	*87, 94*	*85, 93*	*81, 90*	*78, 88*	*70, 87*	*70, 87*	*70, 87*

Figure 2 Kaplan–Meier curve showing the probability survival of MDR-TB patients since the commencement of treatment to end of the treatment follow-up at Gondar University Hospital MDR-TB Treatment Centre, north-west Ethiopia.

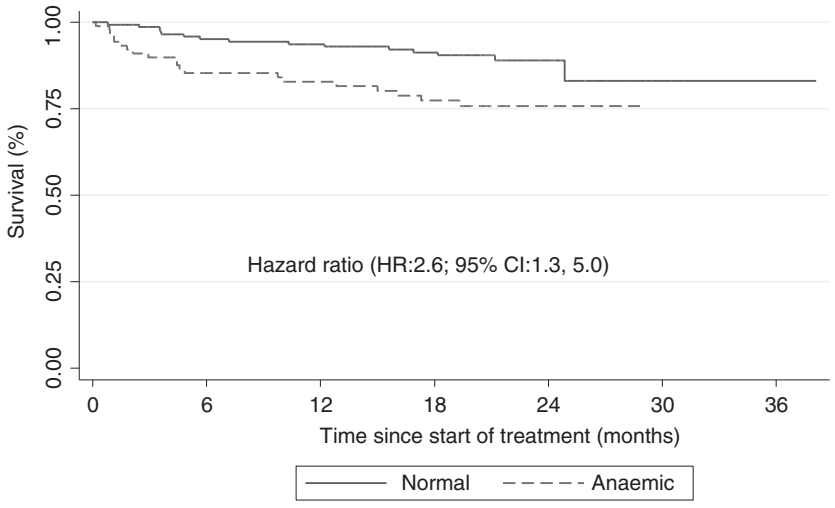
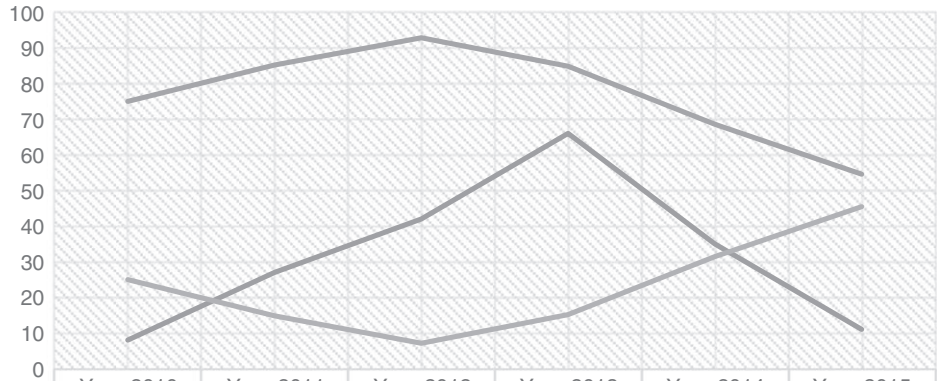


Figure 3 Kaplan–Meier probability of survival curve for anaemic and non-anaemic MDR-TB patients at Gondar University Hospital MDR-TB Treatment Centre, north-west Ethiopia.

which is similar to other resource-constrained countries such as Egypt and India [20, 21] and also high-income countries such as Switzerland (76%) [22], the United Kingdom (70.60%) [23] and the United States of America (78%) [24]. This indicates that good treatment outcomes can be achieved in resource-limited settings. The WHO target of 75% treatment success by 2015 has been met in this cohort [10]. This encouraging outcome in north-west Ethiopia may be due to several reasons, related to the study population and the treatment programme. The patients in our study were generally young, with few serious comorbidities, and they were treated with individualised regimens with a combination of five or six effective drugs. Further, all patients were admitted to the hospital during the intensive phase of treatment and received directly observed therapy. In addition, in the continuation phases of treatment, patients were followed and traced using several strategies: health professionals from the treatment centres visited the patients every month; the patients were appointed monthly to visit the treatment



	Year 2010	Year 2011	Year 2012	Year 2013	Year 2014	Year 2015
Total MDR-TB patients	8	27	42	66	35	11
Succeful treatmetnt outcome	75	85.19	92.86	84.85	68.57	54.55
Poort treatment outcome	25	14.81	7.14	15.15	31.43	45.45

Figure 4 Trends of the number of MDR-TB patients, successful treatment outcome and poor treatment outcome at Gondar University Hospital MDR-TB Treatment Centre, north-west Ethiopia from 2010 to 2015.

initiation site; treatment supporters were assigned from the patient's family to assist the patient with directly observed therapy; and food baskets were provided regularly for the patients.

Despite the high treatment success rate, the proportion of people who died or who failed treatment increased over time. We observed that patients who started treatment between 2010 and 2012 had better treatment outcomes than patients who started treatment between 2013 and 2015. This could be due to the fact that as the number of patients with MDR-TB has increased over time and more MDR-TB treatment centres were opened in other areas, the emphasis given to this treatment centre in terms of resource allocation and quality of service provided to each individual patient may have declined. Although it requires further investigation, this may also be related to a change in susceptibility patterns. Of concern is that our results showed that patients who were previously treated with first-line anti-TB drugs more than four times increased from 3% in 2010 to 34% in 2013.

Another important finding was that both poor treatment outcomes (death or treatment failure) and loss to follow-up mainly occurred in the first 6 months of MDR-TB treatment (i.e. during the intensive phase). There are several possible explanations for this result. Firstly, adverse effects from second-line drugs may be most acute during the intensive phase, thereby interrupting treatment [25]. Secondly, a diagnosis of MDR-TB (and the prospect of taking treatment for 2 years and being hospitalised for 6 months) may create psychosocial problems that led to a poor prognosis, particularly in the early phase of the treatment [26]; and thirdly, late diagnosis of MDR-TB might be responsible, as the majority of our patients were treated with first-line antituberculosis drug several times. This finding suggested that for further improvement of the treatment outcome, early diagnosis of drug-resistant TB is paramount and then effective treatment and management should follow as early as possible before the patient's compliance declines as a result of fatigue with the first-line anti-TB drug treatment without any perceived benefit. It is also necessary to provide psychological counselling for the patients at the time of MDR-TB diagnosis and to closely monitor all patients for adverse drug effects, especially at the early stages of treatment.

Anaemia was one of the factors associated with poor MDR-TB treatment outcomes in our study. Patients who were anaemic were more than two times more likely to have a poor treatment outcome than patients who were non-anaemic. This might be related with late presentation of the patients. Previous studies have also shown that anaemia with or without iron deficiency at TB diagnosis is associated with an increased risk of death [27–29]. In addition to being anaemic, the majority (72%) of the patients in our study were underweight (BMI < 18.5 kg/m^2) and had low average monthly income (around 1.5 USD a day). Early diagnosis and treatment of MDR-TB patients is also suggested to improve the treatment outcome of the patients.

We have also found that farmers were at a higher risk of poor treatment outcome than other types of employees. This could be due to non-adherence to therapy. In

Table 4 Bivariate Cox proportional hazards regression analysis of predictors for time to poor treatment outcome (mortality or treatment failure) among 189 MDR-TB patients

Variables	Patients with poor treatment outcomes*	Unadjusted Hazard ratio	*P*-value
Age			
<18 years	1/21 (4.7)	1.00	–
19–39 years	19/115 (16.5)	3.2 (0.4, 24.0)	0.25
>40 years	15/53 (28.3)	6.0 (0.8, 45.4)	0.08
Sex			
Male	20/116 (17.2)	1.00	–
Female	15/75 (20.5)	1.2 (0.6, 2.4)	0.54
Job			
Employee	3/42 (7.1)	1.00	–
Farmer	15/51 (29.4)	2.7 (1.4, 16.4)	**0.01**
Housewife	6/23 (26.0)	4.2 (1.0, 16.7)	**0.04**
Labourer	8/34 (23.5)	3.6 (0.9, 13.6)	0.06
Student and others	3/39 (18.5)	1.2 (0.2, 5.8)	0.85
Previous TB treatment			
New	5/15 (33.3)	2.6 (0.9, 7.8)	0.07
Once	7/27 (25.9)	1.8 (0.7, 4.8)	0.22
Twice	13/82 (15.8)	1.1 (0.5, 2.5)	0.85
Three and above	10/64 (15.6)	1.00	–
HIV status			
Positive	10/42 (38.8)	1.5 (0.7, 3.0)	0.30
Negative	25/147 (17.0)	1.00	–
BMI			
<18.5 kg/m^2	27/135 [19]	1.4 (0.6, 3.0)	0.41
≥18.5 kg/m^2	8/54 (14.8)	1.00	–
Initial regimen			
Z+E+Cm+Lfx+Eto+Cs	15/108 (13.8)	2.1 (1.0, 4.1)	**0.03**
Z+Cm+Lfx+Eto+Cs	20/80 [24]	1.00	–
Taking vitamin B6			
Yes	24/89 (12.3)	1.00	**0.03**
No	11/99 (24.2)	0.4 (0.2, 0.9)	–
Haemoglobin			
Non-anaemic	15/119 (12.6)	1.00	–
Anaemic**	20/70 (28.5)	2.6 (1.3, 5.0)	**0.006**
Alanine transaminase (ALT)			
Normal	31/175 (17.7)	1.00	–
Elevated	4/14 (28.5)	1.7 (0.6, 4.9)	0.31
Aspartate transaminase (AST)			
Normal	30/151 (19.9)	1.00	–
Elevated	5/38 (13.1)	0.6 (0.2, 1.6)	0.35
Potassium			
Normal	33/183 (18.0)	1.00	–
Elevated	2/6 (33.3)	2.1 (0.5, 8.9)	0.30
Creatinine (mean)	0.65/0.62	1.6 (0.4, 7.0)	0.51
WBC count			
Normal	26/148 (17.5)	1.00	–
Low	7/31 (22.5)	1.23 (0.5, 2.9)	0.57
High	2/10 (20.0)	1.0 (0.2, 4.5)	0.92

Lost to follow-up, still on treatment and transferred out patients were excluded from the bivariate Cox proportional hazard model. Other socio-demographic and clinical variables mentioned in Table 1 were tested but not included in this table because their *P*-value was greater than 0.5.

*Values are number of poor treatment outcome/total number of patients (%).

**Anaemia was defined as having a haemoglobin concentration of less than 120 g/l.

Table 5 Multivariate Cox proportional hazards regression analysis of predictors for time to poor treatment outcome (mortality or treatment failure) among 189 MDR-TB patients

Variables	Patients with poor treatment outcomes	Adjusted Hazard ratio	*P*-value
Age			
≤18 years	1/18	1.00	–
19–39 years	19/98	2.4 (0.2, 23.0)	0.44
≥40 years	15/38	4.2 (0.4, 42.2)	0.22
Job			
Employee	3/39	1.00	–
Farmer	15/36	**4.2 (1.1, 15.9)**	**0.03**
Housewife	6/17	3.8 (0.9, 16.5)	0.07
Daily Labourer	8/26	3.8 (0.9, 15.0)	**0.05**
Student and others	3/36	1.22 (0.2, 7.2)	0.82
Previous TB treatment			
No	5/10	1.00	–
Once	7/20	1.47 (0.4, 5.5)	0.56
Twice	13/69	0.6 (0.2, 1.9)	0.42
Tree times and more	10/54	0.4 (0.1, 1.3)	0.12
BMI			
<18.5 kg/m^2	27/108	1.13 (0.5, 2.7)	0.77
≥18.5 kg/m2	8/46	1.00	–
Initial regimen			
Z+E+Cm+ Lfx+Eto+Cs	15/93	1.3 (0.4, 3.9)	0.67
Z+Cm+Lfx+Eto+Cs	20/60	1.00	–
Taking vitamin B6			
Yes	24/75	2.9 (0.9, 9.2)	0.07
No	11/78	1.00	–
Haemoglobin			
Non-anaemic	15/104	**1.00**	–
Anaemic*	20/50	**2.2 (1.0, 4.9)**	**0.04**

Those variables which were significant in the bivariate Cox proportional model and age were fitted in this model.
*Anaemia was defined as having a haemoglobin concentration of less than 120 g/l.

north-west Ethiopia, previous studies have demonstrated that farmers have delayed healthcare-seeking behaviour, live far from referral hospitals where MDR-TB treatment is offered, have a low socio-economic status and have poor knowledge regarding tuberculosis [30–33]. Further decentralisation of health services may assist those living far from referral hospitals to access and remain on MDR-TB treatment. There may be many other reasons that farmers are at higher risk of poor TB treatment outcomes when compared to other occupations, in addition to confounding factors that we were not able to measure. We acknowledge that farmers may die from causes other than tuberculosis and may have different mortality patterns when compared to other types of employees. We found no difference in poor treatment outcomes according to HIV status. Other studies have also noted this finding [34, 35]. This result is encouraging for those managing MDR-TB services and provides reassurance for patients and advocates who may experience stigma when diagnosed with both diseases.

There were several limitations to this study. Firstly, this study was based on secondary data obtained from patients' medical records and registers. Therefore, potentially important variables such as presence of cavitation on chest radiograph and behavioural factors were not assessed to determine their relationship with poor treatment outcomes. Secondly, in this study those patients who had documented evidence of completion were counted as having a successful treatment outcome, whereas they may have undetected failure of therapy. This may lead to overestimation of the treatment outcome rate in our study, although completed cases in general were few in number (less than 10%). Finally, as the treatment centre was only opened recently, sample size and number of years of data were small and a longer follow-up period will be required to assess longer-term trends in treatment outcomes.

Conclusions

The findings from this study demonstrate that good outcomes for MDR-TB patients can be achieved in a resource-constrained and high TB-burden country. However, poor treatment outcomes have gradually increased overtime. Being a farmer and being anaemic were associated with poor treatment outcomes. This could be confounded by unmeasured factors, and it would be beneficial to assess other risk factors that might affect treatment outcomes, such as co-infection with malaria, poverty and other socio-economic and biological risk factors.

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